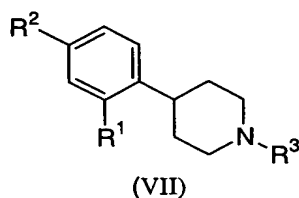


WHAT IS CLAIMED IS:

1. The present invention provides a process for the preparation of compounds of structural formula (VII):



wherein

R¹ is selected from the group consisting of

- (1) CN,
- (2) C(O)OH,
- (3) C(O)-C₁₋₆ alkyl,
- (4) C(O C₁₋₆ alkyl)₂-C₁₋₆ alkyl, and
- (5) C(R⁵)₂N(R⁵)C(O)-C₁₋₆ alkyl;

each R² is independently selected from the group consisting of

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocyclyl,
- (7) -(CH₂)_nC₃₋₇ cycloalkyl,
- (8) fluoride,
- (9) chloride,
- (10) OR⁵,
- (11) -(CH₂)_nN(R⁵)₂,
- (12) -(CH₂)_nC≡N,
- (13) -(CH₂)_nCO₂R⁵,
- (14) NO₂,
- (15) N(R⁵)₂,
- (16) -(CH₂)_nNR⁵SO₂R⁵,

- (17) $-(CH_2)_nSO_2N(R^5)_2$,
 (18) $-(CH_2)_nS(O)_pR^5$,
 (19) $-(CH_2)_nNR^5C(O)N(R^5)_2$,
 (20) $-(CH_2)_nC(O)N(R^5)_2$,
 5 (21) $-(CH_2)_nNR^5C(O)R^5$,
 (22) $-(CH_2)_nNR^5CO_2R^5$,
 (23) $-(CH_2)_nNR^5C(O)$ -heteroaryl,
 (24) $-(CH_2)_nC(O)NR^5N(R^5)_2$,
 (25) $-(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
 10 (26) $O(CH_2)_nC(O)N(R^5)_2$,
 (27) CF_3 ,
 (28) CH_2CF_3 ,
 (29) OCF_3 , and
 (30) OCH_2CF_3 ,

- 15 wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which
 20 they are attached to form a cyclopropyl group;

R^3 is selected from the group consisting of

- (1) $C(O)O$ -phenyl,
 (2) $C(O)O$ - CH_2 -phenyl,
 25 (3) $C(O)O$ -isopropyl,
 (4) $C(O)O$ -isobutyl, and
 (5) $C(O)O$ -ethyl;

each R^5 is independently selected from the group consisting of

- 30 (1) hydrogen,
 (2) C_{1-6} alkyl,
 (3) $-(CH_2)_n$ -phenyl,
 (4) $-(CH_2)_n$ -heteroaryl,
 (5) $-(CH_2)_n$ -naphthyl,
 35 (6) $-(CH_2)_n$ -heterocyclyl,

(7) $-(CH_2)_nC_{3-7}$ cycloalkyl, and

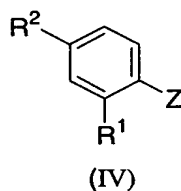
(8) $-(CH_2)_nC_{3-7}$ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy, or two R^5

5 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and $-NC_{1-4}$ alkyl;

comprising the steps of:

(a) preparing a compound of structural formula (IV)

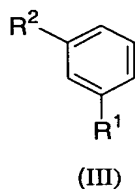


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wherein

R^1 and R^2 are as defined above, and Z is a halogen atom selected from the group consisting of bromide and iodide,

by halogenating a compound of structural formula (III)

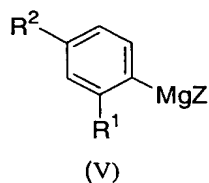


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wherein

R^1 and R^2 are as defined above, and isolating the resulting product;

(b) forming an aryl magnesium halide of structural formula (V)

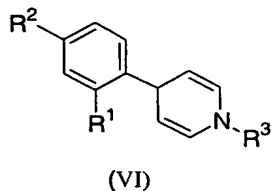


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wherein R^1 , R^2 and Z are as defined above,

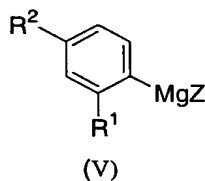
by treating the compound of structural formula (IV) with a magnesium compound;

(c) preparing a compound of structural formula (VI)



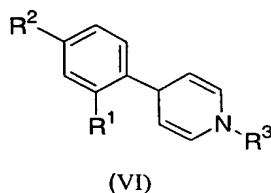
wherein R^1 , R^2 and R^3 are as defined above,

5 by treating the aryl magnesium halide of structural formula (V)



wherein R^1 , R^2 , and Z are as defined above, with a preformed pyridinium ion, and isolating the resulting product;

10 (d) reducing the dihydropyridine double bonds in the compound of structural formula (VI)



wherein R^1 , R^2 and R^3 are as defined above; and

(e) isolating the resulting product.

15

2. The process of Claim 1 wherein R^1 is CN; R^2 is chloride; R^3 is C(O)O-CH₂-phenyl; and Z is bromide.

3. The process of Claim 2 wherein the compound of structural formula (III) is
20 brominated by treatment with a brominating agent in the presence of an acid.

4. The process of Claim 3 wherein the brominating agent is 1,3-dibromo-5,5-dimethylhydantoin.

5. The process of Claim 3 wherein the acid is methane sulfonic acid.

6. The process of Claim 1 step (b) wherein the magnesium compound is a compound of formula (IX)



wherein R^a is selected from the group consisting of isopropyl, cyclohexyl and tert-butyl, and X is selected from the group consisting of chloride, bromide, and iodide.

7. The process of Claim 6 wherein the magnesium compound of formula (X) is isopropyl magnesium chloride.

8. The process of Claim 1 wherein the preformed pyridinium ion of step (c) is formed by treating pyridine, with a chloroformate of formula (X)



wherein R^b is selected from the group consisting of ethyl, isopropyl, isobutyl, phenyl and benzyl, in the presence of a copper compound.

9. The process of Claim 8 wherein the copper compound is copper iodide.

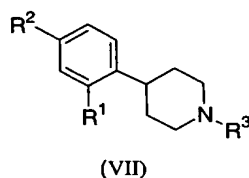
10. The process of Claim 8 wherein the chloroformate of formula (X) is benzyl chloroformate.

11. The process of Claim 1 wherein the dihydropyridine double bonds of compound (VI) of step (d) are reduced by hydrogenation in the presence of a catalyst.

12. The process of Claim 11 wherein the catalyst is $RhCl(PPh_3)_3$.

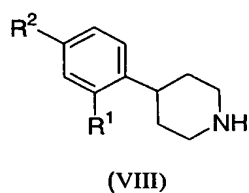
13. The process of Claim 1 further comprising the steps of

(f) cleaving the R³ protecting group in the compound of structural formula (VII)



wherein R¹, R², and R³ are as defined in Claim 1,
to afford a compound of structural formula (VIII)

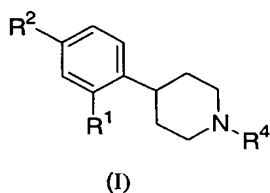
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and isolating the resulting product;

(g) adding a R⁴ protecting group to the free amine (VIII) to form the compound of structural formula (I),

10



wherein R¹, R² are as defined above, and
R⁴ is selected from the group consisting of

- (1) C(O)O-*tert*-butyl,
(2) C(O)O-CH₂-phenyl, and
(3) C(O)O-phenyl; and

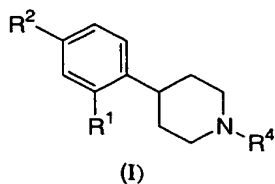
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(h) isolating the resulting product.

20

14. The process of Claim 13 wherein R⁴ is C(O)O-*tert*-butyl.

15. A process for preparing a compound of structural formula (I)



wherein

R¹ is selected from the group consisting of

- (1) CN,
- (2) C(O)OH,
- (3) C(O)-C₁₋₆ alkyl,
- (4) C(O-C₁₋₆ alkyl)₂-C₁₋₆ alkyl, and
- (5) C(R⁵)₂N(R⁵)C(O)-C₁₋₆ alkyl;

each R² is independently selected from the group consisting of

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocyclyl,
- (7) -(CH₂)_n-C₃₋₇ cycloalkyl,
- (8) fluoride,
- (9) chloride,
- (10) OR⁵,
- (11) -(CH₂)_nN(R⁵)₂,
- (12) -(CH₂)_nC≡N,
- (13) -(CH₂)_nCO₂R⁵,
- (14) NO₂,
- (15) N(R⁵)₂,
- (16) -(CH₂)_nNR⁵SO₂R⁵,
- (17) -(CH₂)_nSO₂N(R⁵)₂,
- (18) -(CH₂)_nS(O)_pR⁵,
- (19) -(CH₂)_nNR⁵C(O)N(R⁵)₂,
- (20) -(CH₂)_nC(O)N(R⁵)₂,
- (21) -(CH₂)_nNR⁵C(O)R⁵,
- (22) -(CH₂)_nNR⁵CO₂R⁵,

- (23) $-(\text{CH}_2)_n\text{NR}^5\text{C}(\text{O})\text{-heteroaryl}$,
- (24) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^5\text{N}(\text{R}^5)_2$,
- (25) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^5\text{NR}^5\text{C}(\text{O})\text{R}^5$,
- (26) $\text{O}(\text{CH}_2)_n\text{C}(\text{O})\text{N}(\text{R}^5)_2$,
- (27) CF_3 ,
- (28) CH_2CF_3 ,
- (29) OCF_3 , and
- (30) OCH_2CF_3 ,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein any methylene (CH₂) carbon atom in R² is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R⁴ is selected from the group consisting of

- (1) C(O)O-*tert*-butyl,
- (2) C(O)O-CH₂-phenyl, and
- (3) C(O)O-phenyl; and

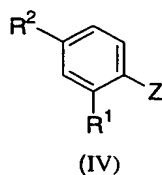
each R⁵ is independently selected from the group consisting of

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) $-(\text{CH}_2)_n\text{-phenyl}$,
- (4) $-(\text{CH}_2)_n\text{-heteroaryl}$,
- (5) $-(\text{CH}_2)_n\text{-naphthyl}$,
- (6) $-(\text{CH}_2)_n\text{-heterocyclyl}$,
- (7) $-(\text{CH}_2)_n\text{C}_{3-7}\text{ cycloalkyl}$, and
- (8) $-(\text{CH}_2)_n\text{C}_{3-7}\text{ bicycloalkyl}$,

wherein alkyl, phenyl, heteroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or two R⁵ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

comprising the steps of:

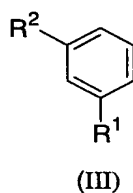
- (a) preparing a compound of structural formula (IV)



wherein

R¹ and R² are as defined above, and Z is a halogen atom selected from the group consisting of bromide and iodide,

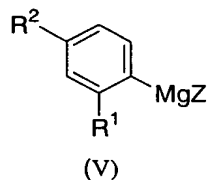
by halogenating a compound of structural formula (III)



wherein

R¹ and R² are as defined above, and isolating the resulting product;

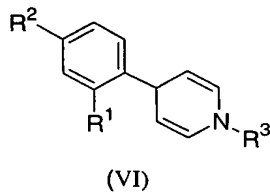
- (b) forming an aryl magnesium halide of structural formula (V)



wherein R¹, R² and Z are as defined above,

by treating the compound of structural formula (IV) with a magnesium compound;

- (c) preparing a compound of structural formula (VI)

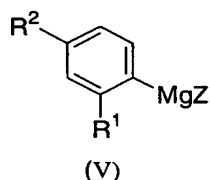


wherein R¹, R² are as defined above, and

R^3 is selected from the group consisting of

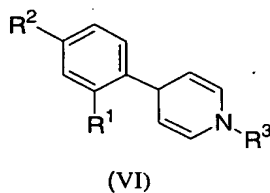
- (1) C(O)O-phenyl,
- (2) C(O)O-CH₂-phenyl,
- (3) C(O)O-isopropyl,
- (4) C(O)O-isobutyl, and
- (5) C(O)O-ethyl,

by treating the aryl magnesium halide of structural formula (V)



wherein R^1 , R^2 , and Z are as defined above, with a preformed pyridinium ion, and isolating the resulting product;

(d) reducing the dihydropyridine double bonds in the compound of structural formula (VI)



wherein R^1 , R^2 and R^3 are as defined above; and

(e) isolating the resulting product.

16. The process of Claim 15 wherein R^1 is CN; R^2 is chloride; R^3 is C(O)O-CH₂-phenyl; R^4 is C(O)O-*tert*-butyl; and Z is bromide.

17. The process of Claim 16 wherein the compound of structural formula (III) is brominated by treatment with a brominating agent in the presence of an acid.

18. The process of Claim 17 wherein the brominating agent is 1,3-dibromo-5,5-dimethylhydantoin.

19. The process of Claim 17 wherein the acid is methanesulfonic acid, trifluoroacetic acid, or sulfuric acid, or a combination thereof.

20. The process of Claim 15 step (b) wherein the magnesium compound is a compound of formula (IX)



wherein R^a is selected from the group consisting of isopropyl, cyclohexyl and tert-butyl, and X is selected from the group consisting of chloride, bromide, and iodide.

21. The process of Claim 20 wherein the magnesium compound of formula (X) is isopropyl magnesium chloride.

22. The process of Claim 15 wherein the preformed pyridinium ion of step (c) is formed by treating pyridine, with a chloroformate of formula (X)



wherein R^b is selected from the group consisting of ethyl, isopropyl, isobutyl, phenyl and benzyl, in the presence of a copper compound.

23. The process of Claim 22 wherein the copper compound is copper iodide.

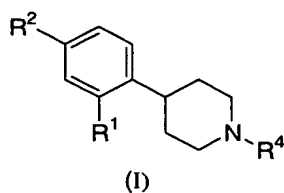
24. The process of Claim 22 wherein the chloroformate of formula (X) is benzyl chloroformate.

25. The process of Claim 15 wherein the dihydropyridine double bonds of compound (VI) of step (d) are reduced by hydrogenation in the presence of a catalyst and an anhydride.

26. The process of Claim 25 wherein the catalyst is Pd/C.

27. The process of Claim 25 wherein the anhydride is *tert*-butyloxycarbonyl anhydride.

28. A process for preparing a compound of structural formula (I)



wherein

R¹ is selected from the group consisting of

- (1) CN,
- (2) C(O)OH,
- (3) C(O)-C₁₋₆ alkyl,
- (4) C(O C₁₋₆ alkyl)₂-C₁₋₆ alkyl, and
- (5) C(R⁵)₂N(R⁵)C(O)-C₁₋₆ alkyl;

each R² is independently selected from the group consisting of

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocyclyl,
- (7) -(CH₂)_nC₃₋₇ cycloalkyl,
- (8) fluoride,
- (9) chloride,
- (10) OR⁵,
- (11) -(CH₂)_nN(R⁵)₂,
- (12) -(CH₂)_nC≡N,
- (13) -(CH₂)_nCO₂R⁵,
- (14) NO₂,
- (15) N(R⁵)₂,
- (16) -(CH₂)_nNR⁵SO₂R⁵,
- (17) -(CH₂)_nSO₂N(R⁵)₂,
- (18) -(CH₂)_nS(O)_pR⁵,
- (19) -(CH₂)_nNR⁵C(O)N(R⁵)₂,
- (20) -(CH₂)_nC(O)N(R⁵)₂,

- (21) $-(CH_2)_nNR^5C(O)R^5$,
 (22) $-(CH_2)_nNR^5CO_2R^5$,
 (23) $-(CH_2)_nNR^5C(O)$ -heteroaryl,
 (24) $-(CH_2)_nC(O)NR^5N(R^5)_2$,
 5 (25) $-(CH_2)_nC(O)NR^5NR^5C(O)R^5$,
 (26) $O(CH_2)_nC(O)N(R^5)_2$,
 (27) CF_3 ,
 (28) CH_2CF_3 ,
 (29) OCF_3 , and
 10 (30) OCH_2CF_3 ,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy, and wherein any methylene (CH_2) carbon atom in R^2 is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl, or two substituents when on the same methylene (CH_2) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

R^4 is selected from the group consisting of

- (1) $C(O)O$ -*tert*-butyl,
 20 (2) $C(O)O$ - CH_2 -phenyl, and
 (3) $C(O)O$ -phenyl; and

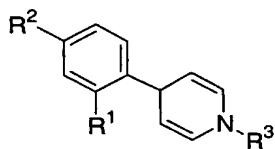
each R^5 is independently selected from the group consisting of

- (1) hydrogen,
 25 (2) C_{1-6} alkyl,
 (3) $-(CH_2)_n$ -phenyl,
 (4) $-(CH_2)_n$ -heteroaryl,
 (5) $-(CH_2)_n$ -naphthyl,
 (6) $-(CH_2)_n$ -heterocyclyl,
 30 (7) $-(CH_2)_nC_{3-7}$ cycloalkyl, and
 (8) $-(CH_2)_nC_{3-7}$ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocyclyl, and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy, or two R^5 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and $-NC_{1-4}$ alkyl;

comprising the steps of:

- (a) reducing the dihydropyridine double bonds in the compound of structural formula (VI)



(VI)

wherein R¹, R² are as defined above, and
R³ is selected from the group consisting of

- (1) C(O)O-phenyl,
- (2) C(O)O-CH₂-phenyl,
- (3) C(O)O-isopropyl,
- (4) C(O)O-isobutyl, and
- (5) C(O)O-ethyl; and

- (b) isolating the resulting product.

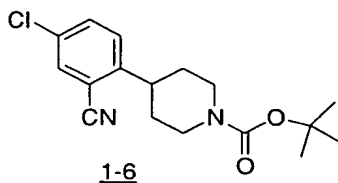
29. The process of Claim 28 wherein R¹ is CN; R² is chloride; R³ is C(O)O-CH₂-phenyl; and R⁴ is C(O)O-*tert*-butyl.

30. The process of Claim 28 wherein the dihydropyridine double bonds of compound (VI) of step (d) are reduced by hydrogenation in the presence of a catalyst and an anhydride.

31. The process of Claim 30 wherein the catalyst is Pd/C.

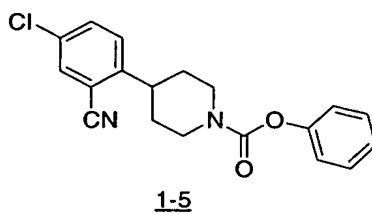
32. The process of Claim 30 wherein the anhydride is *tert*-butyloxycarbonyl anhydride.

33. The compound 1-6



1-6

34. The compound 1-5



5

35. A compound selected from

